Expanding Clinical Impact

For 14 years, Patrick Hwu, M.D., worked in the Tumor Immunology Section of CCR's Surgery Branch developing novel immunological approaches for the treatment of cancer. When he was recruited by the University of Texas M.D. Anderson Cancer Center to lead a new Department of Melanoma Medical Oncology, he saw it as a golden opportunity to bring the therapeutic advances he and his colleagues had made into a brand new clinical setting. Seven years later, Hwu is seeking funding to begin a multicenter randomized clinical trial that he hopes will be pivotal in introducing tumor infiltrating lymphocyte (TIL) therapies as a new standard of care for the treatment of melanoma.

An Immunologist Finds Melanoma

I am now the head of a large melanoma department, but my first interest was immunology. One of the early successes of cancer immunology was the discovery that interleukin-2 (IL-2)—a soluble signaling molecule important for the proliferation of T cells and other lymphocytes that carry out the immune response—had a therapeutic effect in melanoma and kidney cancer patients. So melanoma was an obvious place to start to develop the principles of immunotherapy.

Working with Steven Rosenberg, M.D., Ph.D., at CCR, we developed methods to treat patients with T lymphocytes grown from their own tumors (TILs) and eventually achieved a 50 percent response rate. In a subset of patients, the cancer was effectively

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(*Photo: B. Smith*)

Patrick Hwu, M.D., and members of the Department of Melanoma Medical Oncology at the University of Texas M.D. Anderson Cancer Center.

cured. The therapeutic potential was clear, but the combination of expertise and infrastructure required for its implementation made it difficult for extramural researchers to easily pick up the gauntlet we had thrown down to develop similar clinical research programs. So I accepted the self-imposed challenge to take this technology out to other centers in an attempt to make an impact across the country.

Building a Team

In 2003, M.D. Anderson had just started expanding its basic immunology department and had built a new four-story building with a vision of bringing in translational researchers like myself. In addition, there was a very large clinical program in the melanoma department, but it lacked a matching laboratory research component. It was a wonderful fit for me to bridge these two strong programs. The resulting Melanoma Medical Oncology Department now has a full team of investigators including faculty members devoted to laboratory research, those focused on the clinic, and a few physician-scientists, like me, that straddle both worlds.

The physician-scientist perspective is really critical, in my opinion, for developing a translational program like ours in which you bring insights from the clinic back into the laboratory. Physician-scientists provide the glue to hold the pieces of such a program together and make connections to accelerate translation. For example, we have been able to build a program where we generate T lymphocytes for patient therapy, administer and monitor the therapy through biopsies and unique assays to determine who does and doesn't respond. If I didn't know both the "bench" and "bedside," I wouldn't have been able to organize this program effectively.

Yet, as Chair of a department with trainees at all levels, I realize how extremely challenging it is to train physician-scientists. We are

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really asking people to learn two totally different fields. We are asking people who have already gone through medical school and done their fellowships, "Are you ready to be an intern again?" I'm not sure people realize what a gem CCR really is for training future physician-scientists.

What I appreciate most, especially now that I am no longer there, is that at CCR, there are no pressures to see a lot of patients or get grants. You can focus on the patients that are a part of your research. Investigators are free to perform science without having to worry about many other issues that might fill the day. CCR offers vital protected time for the physician-scientist to mature.

Improving Standard of Care

At M.D. Anderson, we have now treated 30 melanoma patients with TIL therapy and have achieved a 50 percent response rate—identical to what we observed at the NCI. Now we are talking with other centers about doing a multicenter randomized clinical trial in which we can assess the impact of combining TIL with IL-2 therapy, as compared to IL-2 alone. If we can get that trial funded and performed successfully, the cancer treatment we pioneered at CCR will change the standard of care.

Of course, that's not the end of the story. Half the patients we treat don't respond to TIL therapy, and we need to improve those odds. We are also pursuing another line of investigation that we hope to bring to human trials soon. Melanomas produce chemical signals—chemokines—that T lymphocytes don't normally recognize. We are trying to engineer TILs with a receptor that recognizes these chemokines so they can follow the signal to the tumor source. If successful, this is a principle that can be generalized to many other kinds of tumors.

Our chemokine work actually also began at CCR. At the time, I didn't know much about chemokines, but Philip Murphy, M.D., one of the world's experts in chemokines, was just an elevator ride away. All that preliminary data we generated at CCR got me the initial NIH grant to continue this work at M.D. Anderson. Now we're moving it into people.

We do a lot of fantastic clinical trials at M.D. Anderson, but having been "on the outside" for a few years, I do miss the ease of having the NIH's massive Clinical Research Center on my doorstep, where I didn't have to worry about things like insurance approval before putting patients on a protocol or giving them an x-ray. It truly facilitates clinical research. The Center is a major opportunity for the intramural scientists, but it could also be as valuable to extramural scientists who don't have a chance to translate their ideas to the clinic. Think of a sabbatical program in which the Center could host people to develop their idea, start a trial, and spend a couple of years running that trial.

I think there are a lot of opportunities for intramural/extramural collaboration that should be encouraged. For instance, because they don't have a high patient volume, the NIH Clinical Research Center can find it difficult to recruit patients. That is definitely not a problem for places like M.D. Anderson, where patients are seen regardless of the need to fit into a research protocol upfront. So some additional integration might be the best of both worlds.